

Remarks

Applicant appreciates the thorough examination of the present application as evidenced by the Office Action dated February 24, 2004 (hereinafter, "Office Action").

Claims 14, 15, 20, 31-44 and 50-52 are pending in the present application. Applicant further acknowledges with appreciation the indication that in response to the Request for Continued Examination filed by the Applicant on November 21, 2003, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. § 1.114. Also, Applicant hereby confirms that Applicant's election in the parent application is applicable to the present Request for Continued Examination. Further, Applicant has added new claims 53-56. Support for these new claims can be found in the present application at page 11, lines 11-20. Thus, it is Applicant's belief that no new matter is added by the addition of new claims 53-56, and respectfully request entry thereof.

In the present Office Action, claims 14, 15, 20, 31-44 and 50-52 stand rejected. The concerns raised by the Examiner are addressed below.

I. Rejection Under 35 U.S.C. § 103

Claims 14, 15, 20, 31-44 and 50-52 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,863,563 to Scheele (hereinafter, "Scheele") in view of Cropp, Effectiveness of bronchodilators in Cystic Fibrosis, *Am J of Med.* **100(suppl 1A):1A-19S** (hereinafter, "Cropp") and U.S. Patent No. 5,162,348 to Glass (hereinafter, "Glass"). More specifically, the Office Action asserts that "it would have been *prima facie* obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to employ more than one of the known salts disclosed by Scheele in the therapeutical composition, or treating the patient with a bronchodilator before administering the instant composition." Office Action, page 3. Further, in response to Applicant's amendments and remarks submitted November 21, 2003, the Office Action states that "it is generally considered *prima facie* obvious to combine two or more compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very

same purpose . . . As shown by the recited teachings, the instant claims define nothing more than the concomitant use of conventional anti-cystic fibrosis agents with conventional carriers and excipients. Office Action, page 4. Applicant respectfully disagrees with this assertion.

The test of obviousness is what the combined teachings of the references **would have suggested** to those of ordinary skill in the art. *See In re Keller*, 208 U.S.P.Q. 871 (C.C.P.A. 1981) (emphasis added). Moreover, the law requires considering the "whole" of the cited references. *In re Keller* at 881. Additionally, the Court of Appeals for the Federal Circuit has acknowledged that motivation may be lacking when the state of the art at the time the invention in question was discovered pointed researchers in a different direction than the inventor proceeded. *See In re Hedges*, 228 U.S.P.Q. 685 (Fed. Cir. 1986); *W.L. Gore & Assocs., Inc.*, 220 U.S.P.Q. 312 (Fed. Cir. 1983).

Turning specifically to the cited references, Scheele proposes administration of a pH-raising buffer to increase the rate of surfactant by type II alveolar cells. However, as noted in the Office Action, Scheele "does not teach expressly the employment of the combination of salts, or the further employment of bronchodilator in the composition."¹ Office Action, page 3. Cropp and Glass are cited for the proposition that bronchodilators are well known to be useful for treating cystic fibrosis. *See* Office Action, page 3. Consequently, the combination of the cited references do not teach the recitations of the independent claims listed below with highlighted portions for the Examiner's ease in review. Moreover, the teachings of the cited references are incompatible with the teachings of the present application as recited in the claims of the present application.

14. (Previously Presented) A method for treating chronic obstructive pulmonary disease in a subject in need of such treatment, comprising:

administering **at least one osmotically active compound** to an airway surface of the subject **in an amount effective to increase the volume of liquid on the airway surface**, wherein **the at least one osmotically active compound comprises at least one salt; and**

¹ Applicant directs the Examiner's attention to the following boilerplate statement recited later in Scheele: "[t]he pH-raising compositions may be administered in conjunction with other therapeutic compounds (e.g., bronchodilators or antimicrobials) as needed. Scheele, Column 9, lines 47-50.

administering a bronchodilator to said subject prior to or concurrently with said osmotically active compound in an amount sufficient to inhibit bronchoconstriction.

37. (Currently Amended) A method for treating chronic obstructive pulmonary disease in a subject in need of such treatment, comprising **administering at least one salt to an airway surface** of the subject **in an amount effective to increase the volume of liquid on the airway surface**; wherein said **at least one salt comprises a combination of different salts**; and wherein said **combination of different salts have either (i) a same anion or (ii) a same cation wherein at least one of said anion and said cation are non-absorbable in relation to said airway surface.**

51. (Previously Presented) A method for treating cystic fibrosis in a subject in need of such treatment, comprising **administering at least one osmotically active compound to an airway surface** of the subject **in an amount effective to increase the volume of liquid on the airway surface**;

wherein the **at least one osmotically active compound comprises at least one salt; and**
administering a bronchodilator to said subject prior to or concurrently with said osmotically active compound in an amount sufficient to inhibit bronchoconstriction.

Scheele attributes the symptoms of various pulmonary conditions to insufficient secretion of surfactant as a result of an abnormally low pH in the vicinity of the luminal surface of type II alveolar cells. *See* Column 8, lines 33-63. Thus, the solution Scheele proposes is to administer a pH-buffer effective to raise the pH of the aqueous fluid in the luminal microenvironment of the type II alveolar cells for the purpose of increasing surfactant secretion by type II alveolar cells. *See* Column 2, lines 23-30. Scheele further states that "[b]y 'pH-raising buffer', 'pH-raising buffer compound', 'pH-raising composition', 'pH-raising medicament', or 'medicament' is meant a composition which, when contacted with a solution (e.g., the aqueous solution bathing the interior of the alveolus), causes a net increase in the solution pH relative to the solution pH prior to addition of the pH-raising buffer. The pH-raising buffer of the invention is effective to raise the pH of the aqueous film at least about 0.1 pH unit." Column 5, lines 14-22.

Applicant notes that a pH-raising buffer and an osmotically active compound can represent mutually exclusive compounds. A pH-raising buffer acts to lower the $[H^+]$.

As noted in the present application, an osmotically active compound is one that is preferably membrane-impermeable (*i.e.*, essentially non-absorbable) on the airway or pulmonary epithelial surface (*see* Present Application, page 4, lines 5-7), and as shown by the present inventor, **increases the volume of liquid** on the airway surface. As further recited in some of the claims of the present application, the osmotically active compound comprises at least one salt. It is well understood by those skilled in the art that salts can dissociate into ions such that some ions produce no net effect on the pH of an aqueous solution. Other ions can increase the $[H^+]$, and thus, lower pH. Alternatively, some ions can lower $[H^+]$, and thus, increase pH. Thus, osmotically active compounds as described in the present invention can undermine the goal of raising the pH in an environment presented in Scheele. Further, the pH-raising buffers presented in Scheele may not function as osmotically active compounds as disclosed in the present application. Consequently, it is evident that Scheele points researchers in a different direction than the inventor proceeded.

Moreover, the combination of salts as recited in some of the claims of the present application is clearly not taught or suggested by the combination of the cited references in view of the teachings clearly directed in a different direction. Additionally, the cited references fail to teach or suggest the **specific combination of salts** and the likelihood of success of arriving at the present invention by employing the specific combination of salts. A general mention of concomitant usage of therapies with similar indications fails to provide an enabling disclosure to motivate one skilled in the art to arrive at the **specific combination of salts** as recited in some of the claims of the present application.

For at least the reasons discussed above, Applicant respectfully submits that one skilled in the art would not rely upon the proposals of Scheele directed toward using a pH-buffer effective to raise the pH of the aqueous fluid in the luminal microenvironment of the type II alveolar cells in order to arrive at the present invention. Applicant reiterates that the test of obviousness is what the combined

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teachings of the references would have suggested to those of ordinary skill in the art. *See In re Keller*. In view of the teachings of Scheele directed to the use of pH-raising buffers for performing a specific function in comparison to osmotically active compounds and/or salts employed for a distinct physiological purpose, the combination of Scheele, Cropp and Glass would not have suggested to one of ordinary skill in the art a method for treating chronic obstructive pulmonary disease and/or cystic fibrosis in a subject in need of such treatment as recited in the claims of the present application.

Accordingly, Applicant respectfully submits that claims 1, 14, 15, 20, 31-44, 50-52 and new claims 53-56 are not unpatentable under 35 U.S.C. § 103(a) in view of Scheele in further view of Cropp and Glass, and respectfully requests that this rejection be withdrawn.

II. New Claims 53-56

New claims 53-56 are directed to particular categories of bronchodilators. Nothing in the cited references suggests that these bronchodilators could be given in an environment in which pH is altered, as taught by Scheele.

Conclusion

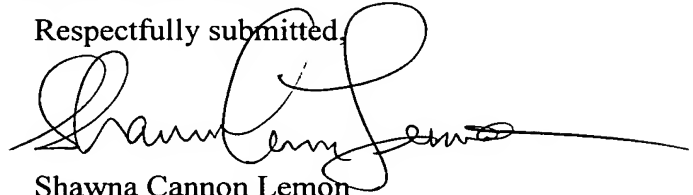
In view of the foregoing amendments and remarks, Applicant respectfully requests that all outstanding rejections to the claims be withdrawn and that a Notice of Allowance be issued in due course. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

It is not believed that any fee(s), including fees for additional claims, are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that additional fees are necessary to allow consideration of this paper, such an extension is also hereby petitioned for

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under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully submitted,



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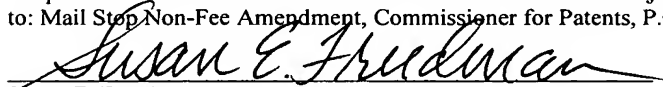
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Susan E. Freedman

Date of Signature: May 24, 2004